Comments in Response to Aspirin Professional Labeling Proposed Changes via Citizen Petition by McNeil Consumer & Specialty Pharmaceuticals

Trials supporting the use of aspirin (ASA) for the prevention of cardiovascular (CV) events have utilized doses optimized for other pharmacologic effects, such as pain and inflammation.[1-5] These higher doses were not based on pharmacokinetics or pharmacodynamics but from historical usage and observations. Since the time of the earlier trials performed in stroke patients, the use of lower dosages has emerged as safe and effective. But it is impossible to conclude that a single daily dosing regimen or even a more limited dosing range would be appropriate for all patients. It is clear however that low doses in the range of 50-325 mg per day for transient ischemic attack (TIA) and stroke and 75-325 mg per day for myocardial infarction (MI) offer a favorable benefit to risk relationship and should continue to be acknowledged in the approved labeling for secondary prevention indications. Furthermore, other dosing paradigms are indicated for the management of acute ischemic events as well as in the prophylaxis of thromboembolic events subsequent to a variety of revascularization procedures.[6] In the case of professional labeling for ASA with physician-directed and monitored use, the approved dosage range should reflect the available evidence allowing for appropriate dosing options. A petition to limit the approved doses in the absence of persuasive randomized clinical trial evidence is scientifically and clinically inappropriate.

Efficacy

Pharmacology

Aspirin interferes with the biosynthesis of cyclic prostanoids, i.e., thromboxane A2 (TXA2), prostacyclin, and other prostaglandins. These prostanoids are generated by the enzymatically catalyzed oxidation of arachidonic acid (AA), which is itself derived from membrane phospholipids.[7,8] Arachidonic acid is metabolized by the enzyme prostaglandin (PG) H-synthase, which through its cyclooxygenase (COX) and peroxidase activities, results in the production of PGG2 and PGH2, respectively. PGH2 is then modified and produces prostaglandins D2, E2, F2a, I2 and TXA2. It is through its inhibition of COX(COX-1) that ASA imparts its antiplatelet effect. The impact of different doses of ASA on this process has demonstrated significant variability.[9-11]

The pharmacologic effects of ASA on the AA pathway may vary related to underlying conditions. Potential modifiers may include smoking[12,13], diabetes[14,15], obesity[16] metabolic syndrome[17] and others.

Factors Potentially Modifying Platelet Aggregation

- Smoking

Platelet activity and platelet aggregation studies suggests that smoking may increase platelet activity, requiring a closer inspection of the dose response relationship of ASA in smokers.

- Authors conclude that smoking-enhanced platelet thrombosis may be an important contributory mechanism for acute coronary events in smokers that is not prevented by aspirin treatment.[12] Catecholamine release and heightened platelet aggregation response to in vivo agonists may contribute to the prothrombotic effects of smoking.
- Research[13] suggests that the increased number of cigarettes smoked per day in healthy habitual smokers leads to an increase in platelet aggregation.

- Diabetes

Recent evidence has suggested that when compared to nondiabetics, diabetics may require higher doses to achieve comparable levels of effectiveness as nondiabetics, suggesting that a range of dose options is important for the management of this population.

- The Primary Prevention Project[14] was a large randomized trial in healthy patients with one or more CV risk factors in which the effects of ASA 100 mg daily was compared to placebo. A post hoc analysis[15] describing the benefits in diabetics and nondiabetics demonstrates significant differences. In nondiabetics the risk for the primary endpoint (stroke/MI/CV death) was reduced by 41% (RR 0.59, CI 0.37-0.94) and in diabetics there was a 10% nonsignificant reduction (RR 0.90, CI 0.50-1.62). The authors suggest that the low dose of ASA as well as other factors may have played a role in the discrepancy.

- A recent *in vitro* trial[16] suggests there is evidence of significantly reduced platelet response to aspirin in diabetic patients compared with healthy controls. Diabetics varied significantly in response to both arachidonic acid and collagen stimulated platelet aggregation.

- Obesity & Metabolic Syndrome

Evidence is emerging that suggests patients with elevated BMI and body weight may require higher doses of ASA for effectiveness. These clinical findings are consistent with what would have been predicted based on the ex vivo platelet aggregation studies described in the Pharmacology Section.

- The Women's Health Study[17] randomized 40,000 healthy female health professionals to ASA 100 mg every other day or placebo for 10 years. Subgroup data stratified by baseline BMI (<25, 25-29, >30) reflects potential differences in response to ASA. Women in the lowest BMI subgroup demonstrated a beneficial response in terms of CV event reduction compared to those in the highest subgroup.

- Recent data also suggests that increased weight is correlated with a poor response to ASA in terms of platelet inhibition.[18] Seventy-five healthy volunteers were administered several different preparations of ASA 75 mg daily for 14 days each. Results suggests that the mean weight for the treatment failures (78.9±9.2 kg) was significantly greater ($p=0.0002$) than those with complete (>99%) inhibition (66.8±8.9 kg) and weight and percent inhibition were strongly correlated ($p<0.0006$, Spearman Rank). Authors conclude that the delivery of a lower daily dose of aspirin by such preparations may result in inadequate response, particularly in overweight subjects.

- A recent study[19] examined the effect of ASA in obese insulin-resistant subject compared to non obese subjects. Before ASA, all doses of arachidonic acid induced complete aggregation. After ASA ingestion, ASA significantly inhibited maximal aggregation more in the non-obese than the obese group. ADP-induced aggregation at

high doses was also significantly less inhibited. In vivo insulin sensitivity and BMI were closely correlated with residual aggregation after ASA administration.

Aspirin Resistance or Variable response

The term aspirin resistance has been used to describe not only an absence or variance of the expected pharmacologic effects of ASA on platelets but also poor clinical outcomes. This variable response based on surrogate markers such as serum thromboxane and platelet aggregability has been the subject of many small investigational studies.[20] Insufficient response has not been clearly correlated with poor outcomes but observational evidence has suggested this possibility.[11,21] Summarized below are several studies that indicate an improved response in patients taking higher doses of ASA. These doses were frequently within the common low dose range (up to 325 mg).

- Helgason et al[22] demonstrated a dose relationship in ASA resistant stroke patients. Escalating the dose of ASA to as high as 1300 mg produced complete inhibition of platelet aggregation in 25 of 28 patients who had only partial response to lower doses ($\leq$325mg).

- Syrbe et al[23] evaluated ASA response via platelet aggregation in 108 CVD patients. 60% of patients were found not responsive to 30mg. Of the remaining 65 patients, 54 were responsive to 100mg and 10 of the final 11 demonstrated response to 300 mg.

- Macchi et al[24] investigated variable responses with respect to platelet polymorphisms. Patients were exposed to 160 mg of ASA for at least one month. 29.6% were found resistant via platelet aggregation measurement. Those resistant patients were given 300 mg of ASA, in which over half responded appropriately.

- Alberts et al[25] reported ASA non-response in cerebrovascular disease patients. Platelet aggregation was measured via PFA-100 device. The study demonstrated a non-response rate of 37% with increased rates in patients who used lower doses (<325 mg), enteric-coated ASA, and in the elderly and women. In those who were found to be not responsive, Alberts reports that increasing the dose to 325 mg BID or TID achieved a therapeutic effect in 15% of patients.

- Recently, Chen et al[26] presented observational data from 468 CAD patients receiving ASA for 4 weeks or more. Platelet aggregation was measured via the VerifyNow device (Accumetrics). A variable response in platelet inhibition was noted. Daily ASA dose $\leq$100 mg was associated with increased prevalence of reduced response compared with 150 mg and 300 mg daily (30.2% vs. 16.7% vs. 0%, p=0.0062).

Pleiotropic effects

While much of the benefit of ASA in the prevention of thromboembolic events can be described by inhibition of platelet thromboxane synthesis, there are possibly other mechanisms with differing dose response curves at play.

Basic research is compatible with the possibility of additional mechanisms operative at higher doses which may lead to greater clinical efficacy. At present, direct comparisons of efficacy with higher aspirin doses in randomized trials, where additional mechanisms may be operative, have not been performed. However, higher doses of aspirin appear to inhibit progression of atherosclerosis.[27-29] Higher doses of aspirin also have been shown to reduce C-reactive protein (CRP)[30], a sensitive marker of inflammation which is an independent predictor of risk of CVD.[31] It is plausible that higher doses of aspirin may add to the antiplatelet benefit of lower doses by additional short term mechanisms including reduction of inflammatory markers, including CRP, soluble intracellular adhesion molecule-1 (s-ICAM 1), tissue plasminogen activator (TPA), and 15-epi-lipoxin A_4, as well as more favorably affecting platelet biomarkers, including p-selectin, beta-thromboglobulin, and thromboxane B2. Additionally, antioxidant effects of aspirin leading to the suppression of lipid peroxidation and reduced vascular tone have also been demonstrated in vivo in experimental animal and humans.[32,33]

Future randomized trials to test whether higher doses of aspirin more favorably affect measures of inflammation, oxidation and vascular tone are necessary to properly explore dose-related non-antiplatelet benefits of ASA

Safety

It is appropriate to manage patients with the lowest effective dose of aspirin as is the case in almost all therapeutic interventions. However, with varying pharmacokinetic and pharmacodynamic profiles, a range of effective doses may be necessary to allow appropriate treatment of an individual patient. Thus, an appropriate risk-benefit assessment should be made for optimal individual patient care.

Gastrointestinal Risk

The most common serious adverse event associated with the use of low dose aspirin for cardiovascular prophylaxis is bleeding from the gastrointestinal tract. As such, this risk must be evaluated and compared to the likely benefit across the indicated dose range.

The GI risks associated with long term ASA therapy have been well defined through numerous randomized trials. The relative risk for GI bleeding approximately doubles with all doses across the low dose range (50-325 mg/d) while the absolute risk remains acceptably low.[34-36] Although the GI risk appears to be dose related for higher doses (>325 mg), the available data do not show evidence of an increased risk within the low dose range.[36] However, sufficient data to appropriately examine these issues are not available. Even a subtherapeutic dose of 10 mg daily substantially inhibits gastric mucosal COX and can cause gastric and duodenal ulceration.[37]

Clinical Trial Evidence For Safety and Efficacy

Randomized clinical trial (RCT) evidence provides the most meaningful data from which to draw conclusions. In keeping with the hierarchy of evidentiary standards, randomized trials will be reviewed first, followed by meta-analyses and finally observational data.

Randomized Clinical Trials

There is limited evidence available from RCTs comparing ASA doses. In fact, there have only been three relevant controlled trials that specifically compared ASA doses. These trials include:

the Dutch TIA trial[38], the UK TIA trial[2] and the Aspirin and Carotid Endarterectomy (ACE) trial.[39] These trials describe the comparative effects of two or more ASA doses in patients who have suffered a TIA or who have undergone a carotid endarterectomy. However, two of these trials are not directly applicable because they compare doses outside the 50-325 mg range. It is important to recognize that there is no prospective, randomized, controlled data in patients with MI or major stroke. Therefore a petition to alter the approved dosing ranges in these populations is scientifically inappropriate and lacks the proper evidence.

- The Dutch TIA trial[38] compared the effects of two doses of ASA (30 mg vs. 283 mg daily) in 3131 patients who had suffered a minor stroke or TIA. The mean follow up was 2.6 years. The frequency of death from vascular causes, nonfatal stroke, or nonfatal myocardial infarction was 14.7% and 15.2% in groups assigned to receive ASA 30mg and 283mg, respectively. There were slightly fewer major bleeding complications in the 30 mg group than in the 283mg group (40 vs. 53, p=NS) and significantly fewer reports of minor bleeding (49 vs. 84).
- The UK TIA trial[2] compared the efficacy of ASA 1200 mg daily, ASA 300 mg daily and placebo in 2435 patients with a history of TIA or minor stroke. Patients were followed for an average of 4 years. Patients receiving either dose of ASA did not differ with respect to cardiovascular endpoints. Both groups experienced similar rates of fatal and nonfatal events. However, the group receiving 1200 mg ASA daily did experience significantly more tolerability issues and GI bleeding events.
- The ACE trial[39] was a randomized, double-blind, controlled trial in 2849 patients scheduled for carotid endarterectomy. Patients were randomized into 4 groups: ASA 81 mg, ASA 325mg, ASA 650 mg, or ASA 1300 mg. Treatment started before surgery and continued for 3 months. The results suggest the greatest benefit is seen in those taking lower doses (81 mg & 325mg) compared to higher doses (650 mg or 1300 mg). But comparing just those taking lower doses reveals a lower event rate for those taking 325 mg daily. Although statistical comparisons were not made between groups a difference in total cardiovascular events including death for those taking 81 mg (61 events) and 325 mg (46 events) was apparent in just 3 months of follow up. GI bleeding complications were identical in the 325mg vs. 81mg groups (8 events vs. 8 events).

As described above, three randomized trials have been performed comparing different dosage regimens of ASA. These trials are limited to the indications of post-TIA and post-carotid endarterectomy prophylaxis. The Dutch TIA trial demonstrated that a very low dose of ASA, which currently lies outside the approved range of doses in the US, appears to be as effective and with a nonsignificant trend towards greater safety than a more traditional low dose of ASA. The UK TIA trial demonstrated that a traditional low dose of ASA (300 mg) is as effective and possibly safer than a dose (1200 mg) which is not in the approved range of doses and is not commonly used in current practice. Finally, the ACE trial demonstrated that lower doses (81 and 325 mg) appear to be more effective and possibly safer than higher doses (650 and 1300 mg). The ACE trial data also demonstrates that there may be meaningful differences in efficacy favoring 325 mg over 81 mg. So, only one relevant RCT directly addresses the issue of safety within the low dose range of 50-325 mg and it shows no clear difference in safety and a potential trend towards increased efficacy with the higher dose (325 mg).

Meta-analyses of RCTs

The Antithrombotic Trialists Collaboration[35] has reviewed over 200 trials involving antiplatelet therapy, the majority of which used ASA. The most recent meta-analysis demonstrates that there are no meaningful differences in effectiveness across the ASA 75-325 mg per day dose range. Indirect comparisons are subject to significant confounding by indication, as patients with many different diagnoses and comorbidities have been studied. This type of analysis is important and may help to generate hypotheses but should not influence the choice of ASA dose for individual indications.

The risk for major bleeding has also been recently assessed via a large meta-analysis.[40] Investigators pooled data from 51 clinical trials with a total of 338,191 patients. They report the rate of major hemorrhage is not different between ASA <100 mg (1.7%) and ASA 100-325 mg (1.7%) daily. Minor bleeds were reported as more than three times as likely in the ASA 100-325 mg (6.5%) group as compared to the ASA <100 mg (1.8%). Clearly these results are inconsistent and represent the confounding that is present in such an analysis. This report is subject to confounding by varied reporting patterns, uniformity of bleeding severity, significant differences in patients characteristics and therapeutic indication. So while this information may help to

generate hypotheses, it can not be relied upon to make dosing recommendations. Such considerations, as mentioned previously, should rely on consistent randomized clinical trial data.

Derry and Loke[36] assessed the incidence of GI hemorrhage associated with long-term ASA use in a meta-analysis of 24 trials. They performed meta-regression to test for a linear relation between daily dose of ASA and risk for GI hemorrhage. The analysis gave a pooled odds ratio of 1.015 per 100 mg dose reduction, with an estimated relative risk reduction in the incidence of GI hemorrhage of 1.5% per 100 mg dose reduction, which was not significant (p=0.3). Based on the data reviewed, it can be concluded that there is no meaningful correlation between GI bleeding and dose.

A recent systematic review of all relevant trials of low dose ASA (75-325 mg) for cardiovascular event prevention shows no difference in the incidence of bleeding events within this dose range (low dose (75-162.5 mg), RR: 1.82, 95% CI 1.53-2.16; high dose (>162.5-325 mg). RR: 1.60, 95% CI 1.09-2.35; Loren Laine, personal communication).

Observational Data

Recently, observational evidence regarding the safety and efficacy of low dose ASA has become available from the Clopidogrel in Unstable angina to prevent Recurrent Event (CURE)[41] and the Blockade of the glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO)[42] trials. These trials had as their primary goal the evaluation of the effectiveness of novel antithrombotic agents other than ASA and as a result, the allocation to ASA dose was not randomly assigned. The dose of ASA was left to the discretion of the investigator. It is important to consider that ASA data reported on from both the CURE and BRAVO trials are subject to significant confounding. Patients in these trials varied by indication, baseline comorbidities and region.

- The CURE trial[41] was designed to assess the benefits and risks of adding clopidogrel to ASA in the treatment of patients with acute coronary syndrome. Patients taking low dose ASA were randomized to receive either clopidogrel or placebo (n=12,562). Follow-up lasted 3 – 12 months. A subsequent post hoc analysis[43] compared the effects of different doses of ASA in both the placebo and active groups. Patients were arbitrarily divided into three groups

based on their dose of ASA at study entry: ≤ 100 mg, 101-199 mg and ≥200 mg. The findings suggest that the incidence of major bleeding complications increases with increasing ASA dose (with or without the addition of clopidogrel). In the placebo group, there was an increase in risk for major bleeding complications from the lowest to the highest ASA dose groups (1.9% vs. 3.7%). The results also suggests a lower rate for the composite primary endpoint (stroke/MI/CV death) in the lowest dose vs. the highest dose (10.5% vs. 13.6%).

- The BRAVO trial[42] was a large-scale evaluation of an orally administered IIb/IIIa inhibitor, lotrafiban, in coronary and cerebrovascular disease. 9190 patients taking low dose ASA were randomized to receive lotrafiban or placebo for up to 2 years. Observations from the placebo group demonstrate differences among two ASA subgroups (ASA 75-162 mg and ASA >162 mg daily). Rates of bleeding complications were higher among those taking the higher doses of ASA, but total ischemic events did not differ. Notably, the rate of mortality was higher among those taking the lower dose. Aronow and colleagues[44] recently presented a subsequent covariate analysis of the ASA data from the BRAVO trial. The analysis suggests that in all patients the rate of mortality is significantly lower among those randomized to ASA dose ≥ 162 mg daily (2.1% vs. 3.2%, p=0.001). Also, there was a significant increase in serious bleeding among those taking the higher doses (6.1% vs. 4.8%, p=0.008).

While the BRAVO and CURE trials represent opportunities to observe the potential effects of different doses of ASA in patients at high risk for CV events, they should remain hypothesis generating. In CURE, the fact that low dose ASA patients not only had fewer major bleeds but fewer CV events, which would not be expected, further supports the hypothesis that lower risk patients were preferentially prescribed low dose ASA. When compared, the BRAVO and CURE trials vary significantly. The most notable difference is with respect to efficacy, suggesting therefore, that the benefit/risk ratios must be considered.

In both trials the dose of ASA used was only recorded at study entry and changes were not recorded or tracked. Additionally, the ASA data is nonrandomized and is subject to significant

confounding due to differences in indication, comorbidities and region. Observations such as these should therefore serve as the basis, not substitutes for, randomized, controlled trials.

Recent Trials Using Higher Doses of ASA

Recently two large randomized trials in stroke patients have evaluated the benefits and risks of higher dose ASA versus standard comparators.

- The African American Antiplatelet Stroke Prevention Study (AAASPS)[45] was a randomized, double-blind, multicenter trial of 1809 black men and women with recent noncardioembolic stroke conducted between 1995 and 2002. Follow up lasted 2 years. Patients were randomized to receive either ASA 650 mg daily or ticlopidine 500 mg daily. The primary endpoint (recurrent stroke/MI/vascular death) occurred in 112 patients (12.3%) taking ASA. Major GI bleeding occurred in 8 ASA patients (0.9%). Importantly, ASA 650 mg daily was found to be slightly more effective and safer than ticlopidine.
- The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID)[46] trial was a randomized trial comparing ASA 1300mg daily to warfarin therapy (INR 2-3) in patients with TIA or stroke caused by stenosis of a major intracranial artery. The study was conducted between 1999 and 2003 and follow up lasted for 1.8 years. The composite endpoint of stroke/MI/vascular death occurred in 66 patients (23.6%) taking ASA. Major GI bleeding occurred in 6 ASA patients (2.2%). The trial was stopped by the DSMB because of increasing safety concerns related to warfarin use compared to ASA. ASA 1300 mg was determined to be safe and effective in this population.

As evidenced by the trials above, higher doses of ASA ($\geq$650 mg) in certain stroke populations have demonstrated favorable benefit/risk ratios. It is important to consider that these trials, conducted by leading investigators and institutions chose to use higher doses of ASA despite the evidence that lower doses may be acceptable. Clearly, there remains belief within the stroke physician community that high doses of ASA are important and valuable to the care of these populations.

Guidelines & Physician Practice

Guidelines from the ACC/AHA support the use of ASA 75-325 mg daily for the prevention of subsequent events and death in patients who have suffered a myocardial infarction or angina[47]. Additionally, the AHA supports the daily use of ASA in the range of 50-325 mg for patients with TIA or mild stroke who do not have atrial fibrillation or moderate to severe carotid stenosis[48]. Guidelines also support the use of ASA 162-325 mg for treatment of acute myocardial infarction[49] and ASA 100-325 mg daily for patients following a coronary artery bypass procedure[50].

Further, physician practice as seen in recent market research and survey data support physician use and comfort with the current ASA dose range. In a survey of 300 physicians[51], 42% say they most often recommend 325 mg for patients who have previously suffered a cardiovascular event. When asked why they chose 325 mg, the response given most often was related to the efficacy of 325 mg. The publication and broad acceptance of practice guidelines and robust physician survey data represents agreement and concurrence with the currently approved dosage range.

Conclusion

It seems clear that across the entire range of possible ASA doses (up to 4000mg daily) there is a dose-related gastrointestinal bleeding effect. However, there is no meaningful direct comparative evidence that the differences between ASA 75-150 mg and 150-325 mg with respect to safety are clinically significant. The only studies evaluating this question prospectively have used comparative doses outside this range or lack the size and strength to draw firm conclusions. Prospective and observational comparisons of doses within the low dose range have been inconsistent with respect to efficacy and at least two meta-analyses and one randomized comparison do not support safety differences between ASA regimens in the low dose range. Therefore, based on the lack of randomized clinical trial evidence and the emerging awareness of the potential benefits of higher doses of ASA in certain patient populations it would be scientifically and clinically inappropriate to modify the dosage range for ASA for the currently approved professional indications.